DEPARTMENT OF HEALTH & HUMAN SERVICES

MAR 31 2003

Food and Drug Administration
Rockville MD 20857

Helen Torelli, Esq.
Office of General Counsel
Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933-7002

Re: Docket Nos. 02P-0252/PRC1, 02P-0191/PRC1, & 01P-0495/PRC1

Dear Ms. Torelli:

On June 11, 2002, the Food and Drug Administration (FDA) issued a response to three citizen petitions seeking approval of abbreviated new drug applications (ANDAs) for tramadol hydrochloride 50 milligram (mg) tablets (tramadol). The citizen petitions were granted in part and denied in part. In a letter dated June 20, 2002, Johnson & Johnson Pharmaceutical Research and Development, L.L.C. and Ortho-McNeil Pharmaceutical, Inc. requested reconsideration of our June 11 response to the tramadol petitions.[1] FDA docketed this request as a petition for reconsideration under 21 CFR § 10.33 in each of the dockets referenced above. For the reasons that follow, FDA reaffirms the June 11, 2002, decision.

Your request for reconsideration raises a number of objections to FDA's approval of ANDAs for tramadol with certain protected labeling omitted. You ask FDA to conclude that the 25-milligram (mg), 16-day starting regimen for tramadol is superior to the 10-day, 50-mg starting regimen. The agency has reviewed the issues you raise and the record in this matter. We believe that most of the points raised in your petition are adequately addressed in our June 11, 2002, response. The approved ANDA labeling meets the requirements of FDA's regulation at 21 CFR § 314.127(a)(7), which provides that the labeling of a generic drug may differ from the labeling of a reference listed drug when, among other things, "aspects of the listed drug's labeling are protected by patent, or by exclusivity, and such differences do not render the proposed drug product less safe or effective than the listed drug *for all remaining, non-protected conditions of use*" (emphasis added).

The agency affirms that generic tramadol products as labeled according to FDA's earlier decision are no less safe or effective than the listed drug for the remaining, nonprotected conditions of use. Specifically, tramadol drug products with labeling omitting the protected 25-mg, 16-day titration schedule are no less safe and effective than Ultram for use according to the titrated and nontitrated 50-mg dosing schedules for which they are labeled.

[1] A subsidiary of Johnson & Johnson, R.W. Johnson Pharmaceutical Research Institute, holds the NDA for Ultram, the listed drug referenced in the ANDAs.

02P-0191

PAV2

Our June 11, 2002, response stated that "it may be that the protected schedule results in decreased efficacy by delivering a subtherapeutic dose for up to 16 days." (Petition response at 8). Your request for reconsideration states that "[t]he suggestion that dosing on all 16 days of the regimen may be subtherapeutic is inexplicable." (Request for reconsideration at 5.) Our comment regarding subtherapeutic dosing is quite simple in its basis: we looked at the patient with chronic pain requiring analgesia 24 hours a day and, noting that 50 mg is the minimally effective single dose, we looked to see at what point the patient receives 50 mg at least every 6 hours. Under the approved 25-mg titration regime it is not until day 16 that a patient is receiving the 50 mg per dose every 6 hours (200 mg/day).[2]

FDA also has reviewed your comments regarding the single line graph included in the ANDA tramadol drug product labeling. FDA believes that even without the information on the 25 mg 16-day titration schedule, this graph provides health care providers valuable information regarding the tolerability of tramadol.

The review of ANDAs for tramadol hydrochloride tablets presented to FDA relatively new issues involving protected labeling for conditions of use other than indications. This case shows that it is a very fact-specific inquiry determining whether an ANDA may be approved under the standard of 21 CFR § 314.127 without labeling that addresses a nonindication condition of use. These issues will continue to be resolved on a case-by-case basis depending on whether the legal and medical standards for ANDA approval are satisfied given the specific facts presented. In this case, FDA concluded that the legal and medical standards for approval were satisfied, and the agency affirms that the tramadol hydrochloride products approved without the 25-mg titration schedule are as safe and effective as Ultram under the same conditions of use.

Finally, the agency appreciates your offer to waive your exclusivity and patent rights as to the 16-day titration regimen in the event that FDA were to require generic tramadol products to carry that titration regimen labeling. FDA has concluded that the 16-day regimen is not required for generic tramadol. However, if you were to waive your exclusivity and patent protection, FDA would then require the ANDA sponsors to conform their labeling to that of Ultram, your tramadol hydrochloride product. Such an outcome would fully address your concerns about safety and the public health.

Sincerely yours,

William K. Hubbard
Associate Commissioner
for Policy and Planning

[2] The titration scheme results in the following daily doses: 25 mg/day on days 1-3; 50 mg/day on days 4-6; 75 mg/day on days 7-9; 100 mg/day on days 10-12; 150 mg/day on days 13-15, and 200 mg/day on day 16.